REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 8-11, 15-18, 35-44, 46 and 47, the only claims pending and under examination in this application.

Claim Rejections - 35 USC § 102

Claims 8-11, 15-18, 35, 37, 39, 40 and 44 are rejected under 35 U.S.C. § 102(b) as being anticipated by Jiang et al. (Carcinogenesis 1993 14:67).

With regard to anticipation of an invention, MPEP § 2131 states:

> "A claim is anticipated only if **each and every element** as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). *(emphasis added)*

The claimed invention is drawn to methods of inhibiting angiogenesis or tumor growth in a host having a condition associated with unwanted angiogenesis or a neoplastic condition by administering to the subject an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent (e.g., cyclosporin). In other words, the invention is drawn to treating an established condition having unwanted angiogenesis or tumor growth.

As discussed in previous responses, Jiang et al. is concerned with testing the ability of FK506 to prevent papilloma formation in an animal. The experimental system used by Jiang et al. is a mouse model in which repeated application of TPA to the skin of CD-1 mice (twice weekly for 22 weeks) results in papilloma formation. Jiang et al. compared papilloma formation between control mice (treated with TPA alone) or mice in which FK506 was applied to the skin 15 minutes prior to each application of TPA and found that in the FK506treated animals, the number and frequency of papilloma formation was reduced.

In interpreting this data, the Examiner asserts that Jiang et al. has inherently demonstrated that the anti-angiogenic activity of FK506 is effective in treating a subject with a condition associated with unwanted angiogenesis or in preventing tumor growth, thus anticipating the claimed invention. The Examiner specifically

cites Figure 1 as demonstrating this teaching, noting that after week 15 of the experiment, the mice in the FK506 treated group have developed papillomas and that they develop fewer papillomas than their untreated control counterparts.

In response, the Applicants again submit that while Jiang et al. may demonstrate that FK506 slows TPA-induced papilloma formation, they fail to show that the application of FK506 has any effect on existing papillomas, as asserted by the Examiner. In fact, the Applicants submit that the data in Figure 1, which the Examiner cites as anticipatory to the claimed invention, merely demonstrates that the rate of papilloma formation is delayed in the FK506-treated group: it does not show an inhibitory effect of FK506 on papilloma growth.

Specifically, both of the FK506-treated groups have an increase in the number of papillomas formed during the course of the experiment in Figure 1. It is only the rate of formation of papillomas that is altered. As such, if the experiment in Figure 1 were carried out for a long enough period of time (i.e., if the data were extrapolated), the FK506-treated cohorts would continue to acquire papillomas and might even achieve the same number as the control cohort. As such, the data in Figure 1 is clearly insufficient to anticipate the claimed invention. To do so, Jiang et al. would have to determine experimentally if FK506 has any effect on papilloma growth, not just papilloma formation. To address this issue using their experimental system, Jiang et al. could have performed an experiment in which pre-existing TPA-induced papillomas were studied for their growth characteristics in the presence and absence of FK506 without further administration of TPA. However, this experiment was not done.

Therefore, the Applicants again submit that it is entirely possible and in no way inconsistent with the asserted teachings of Jiang et al. that FK506 has no effect on the growth of TPA-induced papillomas. Without addressing this experimentally, it is simply impossible for Jiang et al. to anticipate the claimed invention. While the Examiner states that the Applicants' opinion on this matter carries no evidentiary weight, the Applicants respectfully submit that it is not the duty of the Applicants to provide evidence in making the factual observation that the data provided in Jiang et

al. fails to anticipate the claimed invention. The Applicants are simply stating that one of skill in the art could not draw a conclusion regarding the effect of FK506 on the growth of TPA-induced papillomas because the appropriate experiments were not performed. Indeed, Jiang et al. are clearly cognizant of the scope of their experiments as they do not make any claim as to the effect of FK506 on papilloma growth. Rather, Jiang et al. restrict their interpretation to the effect of FK506 on TPA-induced papilloma formation.

In addition, the Applicants submit that the Examiner has failed to establish a case of anticipation based on inherency. With regard to inherency, MPEP §2112 states:

> IV. EXAMINER MUST PROVIDE RATION-ALE OR EVIDENCE TENDING TO SHOW INHERENCY
> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities.** The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). **(emphasis added)**

The Applicants submit that the Examiner's case of inherency is deficient because no evidence has been provided to establish that the ability of FK506 to reduce the rate of papilloma formation as disclosed by Jiang et al. is related to its anti-angiogenic activity. The Examiner merely has stated that this may be the mechanism of action. Without such evidence, one of skill in the art would not necessarily recognize from the experiments of Jiang et al. that FK506 acts as an angiogenesis inhibitor. Indeed, it is entirely possible that the mechanism of action of FK506 in the model system of Jiang et al. is not related to angiogenesis in any way. Therefore, the entirety of the Examiner's inherency rejection is based on possible modes of action of FK506 and not on evidentiary analysis, and as is made clear from

the excerpt above, an anticipation rejection based on inherency "may not be established by possibilities or probabilities."

In light of the discussion above, the Applicants respectfully request withdrawal of this rejection.

Claim Rejections - 35 USC § 103

Claims 36-44, 46 and 47 have been rejected under 35 U.S.C. § 103(a) as being obvious over Jiang et al. (Carcinogenesis 1993 14:67) in view of Flanagan et al. (Nature 1991 352:803).

As discussed above, Jiang et al. fails to teach or suggest administering an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent to a subject having a condition of unwanted angiogenesis or a neoplastic condition for the purpose of inhibiting angiogenesis or tumor growth in the subject as is claimed in the present application. As Flanagan et al. is cited solely for its asserted teaching that FK506, cyclosporin and rapamycin have similar biologic activity, it fails to fill the fundamental deficiencies in Jiang et al. in making the claimed invention obvious.

Therefore, the Applicants submit that Claims 36-44, 46 and 47 are not obvious under 35 U.S.C. § 103(a) over Jiang et al. in view of Flanagan et al. and respectfully request withdrawal of this rejection.

CONCLUSION

In view of the amendments and remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 833-7770. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-201.

Respectfully submitted,

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